

CHRONIC TOXICITY SUMMARY

NAPHTHALENE

(*naphthene*, NCI-C5290, *albocarbon*, *dezodorator*, *moth balls*, *moth flakes*, *tar camphor*, *white tar*, *naphthalin*, *naphthaline*)

CAS Registry Number: 91-20-3

I. Chronic Toxicity Summary

Inhalation reference exposure level

9 mg/m³ (2 ppb)

Critical effect(s)

Respiratory effects (nasal inflammation, olfactory epithelial metaplasia, respiratory epithelial hyperplasia) in mice

Hazard index target(s)

Respiratory system, blood systems

II. Physical and Chemical Properties (HSDB, 1995; 1999 except as noted)

Description

White crystalline powder; odor of mothballs

Molecular formula

C₁₀H₈

Molecular weight

128.6 g/mol

Density

4.42 g/cm³ @ 20°C

Boiling point

218°C

Melting point

80.5 °C

Vapor pressure

0.078 torr @ 25°C (Sonnenfeld *et al.*, 1983); 0.10 torr @ 27°C (CRC, 1994)

Conversion factor

5.26 µg/m³ per ppb at 25°C

III. Major Uses or Sources

Naphthalene is a natural constituent of coal tar (approximately 11%) (HSDB, 1995). It is present in gasoline and diesel fuels. Naphthalene is used as a moth repellent, though this use is decreasing in favor of p-dichlorobenzene (HSDB, 1995). It has also been used in the manufacture of phthalic anhydride, phthalic and anthranilic acids, naphthols, naphthylamines, 1-naphthyl-n-methylcarbamate insecticide, beta-naphthol, naphthalene sulfonates, synthetic resins, celluloid, lampblack, smokeless powder, anthraquinone, indigo, perylene, and hydronaphthalenes (NTP, 1992; HSDB, 1995). The statewide emissions from facilities reporting under the Air Toxics Hot Spots Act in California, based on the most recent inventory, were estimated to be 164,459 pounds of naphthalene (CARB, 1999).

IV. Effects of Human Exposure

Nine persons (eight adults and one child) were exposed to naphthalene vapors from several hundred mothballs in their homes. Nausea, vomiting, abdominal pain, and anemia were reported (Linick, 1983). Testing at one home following the incident indicated an airborne naphthalene concentration of 20 ppb (105 $\mu\text{g}/\text{m}^3$). Symptoms abated after removal of the mothballs.

Workers occupationally exposed to naphthalene fumes or dust for up to five years were studied for adverse ocular effects (Ghetti and Mariani, 1956). Multiple pin-point opacities developed in 8 of 21 workers. Vision did not appear to be impaired.

Cataracts and retinal hemorrhage were observed in a 44 year old man occupationally exposed to powdered naphthalene, and a coworker developed chorioretinitis (van der Hoeve, 1906).

Wolf (1978) reported that a majority of 15 persons involved in naphthalene manufacture developed either rhinopharyngolaryngitis and/or laryngeal carcinoma.

Ingestion of naphthalene or p-dichlorobenzene mothballs is a frequent cause of accidental poisoning of children (Siegel and Wason, 1986). Infants exposed to naphthalene vapors from clothes or blankets have become ill or have died (U.S. EPA, 1990). The effects in infants have been associated with maternal naphthalene exposure during gestation (U.S. EPA, 1990).

Deaths have been reported following ingestion of naphthalene mothballs. A 17-year old male ingested mothballs, developed gastrointestinal bleeding, hematuria, and coma, and died after five days (Gupta *et al.*, 1979). A 30-year old female ingested 30 mothballs and died after five days (Kurz, 1987).

Acute hemolytic anemia was reported among 21 infants exposed to naphthalene vapors from nearby mothball-treated materials (Valaes *et al.*, 1963). Increased serum bilirubin, methemoglobin, Heinz bodies, and fragmented red blood cells were observed. Kernicterus was noted in eight of the children, and two of the children died. Ten of these children had a genetic deficiency in glucose-6-phosphate dehydrogenase.

A 12-year old male ingested 4 g of naphthalene and 20 hours later developed hematuria, anemia, restlessness, and liver enlargement (Manchanda and Sood, 1960). The patient recovered after 8 days.

A 69-year old female developed aplastic anemia two months after several weeks exposure to naphthalene and p-dichlorobenzene (Harden and Baetjer, 1978).

V. Effects of Animal Exposure

Male and female B6C3F1 mice were exposed to naphthalene (>99% pure) vapor for 6 hours per day, 5 days per week over 104 weeks (NTP, 1992). Concentrations used were 0 (150 mice), 10 (150 mice), or 30 ppm (300 mice) naphthalene. (Table 1). Lesions were observed in the nose and lungs of exposed mice, including increased incidences of chronic nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia.

Table 1. Incidence of respiratory tract lesions in mice (male and female combined) chronically exposed to naphthalene vapors (NTP, 1992).

	0 ppm	10 ppm	30 ppm
Nasal inflammation	3/139	34/134	108/270
Olfactory epithelial metaplasia	0/139	131/134	269/270
Respiratory epithelial hyperplasia	0/139	131/134	269/270

CD-1 mice were administered 5.3, 53, or 133 mg/kg/day naphthalene by gavage over 90 days (Shopp *et al.*, 1984). The only effect noted was inhibition of aryl hydrocarbon hydroxylase activity. No increase in mortality or changes in body weight were noted. Reduced spleen weights were noted in females exposed to the highest dose. No changes were noted in serum enzyme levels or electrolytes. The researchers did not conduct a histopathological examination.

B6C3F1 mice were administered 200 mg naphthalene/kg/day by gavage for 5 days per week over 13 weeks. No adverse effects were observed (U.S. EPA, 1990).

Developmental effects of naphthalene ingestion in Sprague-Dawley CD rats was studied by Navarro and associates (1991). The lowest dose tested (50 mg/kg/day by gavage) was associated with signs of CNS depression for the first 3 days. Fetal growth, survival, and morphological development were not significantly affected at 450 mg/kg/day compared with control animals, although a trend toward decreased fetal weight and increased malformations was observed.

Harris and associates (1979) intraperitoneally administered 395 mg/kg/day naphthalene to Sprague-Dawley rats over days 1 through 15 of gestation. Fetuses had a 50% increase in incidence in delayed cranial ossification and heart development.

New Zealand white rabbits were given 0, 40, 200, or 400 mg/kg/day by gavage over days 6 through 18 of gestation (U.S. EPA, 1986a). A dose-dependent increase in grooming, vocalization, aggression, diarrhea, dyspnea, and ocular and nasal discharge were noted at all doses. No statistically significant increase in malformations or developmental abnormalities was observed.

Sprague-Dawley rats were administered 0, 100, 300, or 1000 mg/kg/day of naphthalene via dermal application (U.S. EPA, 1986b). No effects were reported at 100 or 300 mg/kg/day. At the high dose a slight decrease in testes weight was noted.

VI. Derivation of Chronic Reference Exposure Level (REL)

<i>Study</i>	NTP (1992)
<i>Study population</i>	B6C3F1 mice (75 or 150/group/sex)
<i>Exposure method</i>	Discontinuous whole-body inhalation exposures to 0, 10, or 30 ppm naphthalene vapor
<i>Critical effects</i>	Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia

<i>LOAEL</i>	10 ppm (96% incidence for males and 100% incidence for females)
<i>NOAEL</i>	Not observed
<i>Exposure continuity</i>	6 hours/day for 5 days/week
<i>Average experimental exposure</i>	1.8 ppm (10 ppm x 6/24 x 5/7) for LOAEL group
<i>Exposure duration</i>	104 weeks
<i>Subchronic uncertainty factor</i>	1
<i>LOAEL uncertainty factor</i>	10
<i>Interspecies uncertainty factor</i>	10 (see below)
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	1000
<i>Inhalation reference exposure level</i>	0.002 ppm (2 ppb, 0.009 mg/m ³ , 9 µg/m ³)

The NTP study was chosen for the REL derivation since it is the only available lifetime animal inhalation bioassay and because no adequate epidemiological studies of long-term human exposure are available. The study was judged to be of adequate study design. The complete lack of nasal effects among control animals and the nearly total effect among animals exposed at 2 different concentrations strongly indicates a causal relationship between naphthalene exposure and nasal effects. The effects seen are consistent with those reported among exposed workers, who developed rhinopharyngolaryngitis or laryngeal carcinoma (Wolf, 1978). However, the hematological effects observed in humans have not been reported in laboratory animals, which raises the possibility that humans may be significantly more sensitive to naphthalene.

The most important limitation of the study is that the lowest concentration tested caused adverse effects in most (≥96%) of the animals tested. Thus the study amply demonstrates the risk of lifetime exposures to 10 ppm, but is uninformative regarding the concentration-response relationship at lower concentrations. Only a general assumption can be drawn on the magnitude of uncertainty factor needed to predict a concentration at which adverse effects would most likely not be observed. Lacking specific guidance or relevant research for this situation, the default 10-fold factor was applied. U.S. EPA also used the NTP study to develop its RfC of 3 µg/m³ with slightly different assumptions and a cumulative uncertainty factor of 3000 (U.S. EPA, 2000). OEHHHA followed the U.S. EPA precedent in using an intraspecies UF of 10 for naphthalene, rather than using the HEC/RGDR approach. According to U.S. EPA (2000), because of its low water solubility and low reactivity, naphthalene-related effects on the nasal epithelium are expected to result following absorption of naphthalene and its metabolism to reactive oxygenated metabolites, not from direct contact. This is supported by data on naphthalene metabolism indicating that toxic effects on the respiratory tract are due to a naphthalene metabolite that may be formed either in the liver or in the respiratory tract. Necrosis of bronchial epithelial (Clara) cells in mice and necrosis of olfactory epithelium in mice, rats, and hamsters occur following intraperitoneal injection of naphthalene. The nasal effects from inhalation exposure to naphthalene were considered to be extra-respiratory effects of a category 3 gas (U.S. EPA, 1994). The assumption is made that nasal responses in mice to inhaled naphthalene are relevant to humans; however, it is uncertain that the RfC for naphthalene based on nasal effects will be protective for hemolytic anemia and cataracts, the more well-known effects from naphthalene exposure in humans.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the REL for naphthalene include the large number of animals in the key study on which the REL is based and the 2 year length of the study. The limitations include the very high incidence of lesions at the lowest level tested in the key study, the absence of a NOAEL in the key study, the absence of other animal studies by the inhalation route, and the paucity of human data.

VIII. References

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